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# UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new computer applications under 37 CFR 1.53(d))

Attorney Docket No.	LEX-0091-USA
First Inventor	C. Alexander Turner, Jr. et al.
Title	Novel Human Notch Ligand Proteins and Polynucleotides
Express Mail label No.	EL672756285US

## APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

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NOVEL HUMAN *NOTCH* LIGAND PROTEINS AND  
POLYNUCLEOTIDES ENCODING THE SAME

The present application claims the benefit of U.S.

5 Provisional Application Number 60/165,959 which was filed on  
November 17, 1999 and is herein incorporated by reference in its  
entirety.

1. INTRODUCTION

The present invention relates to the discovery,  
10 identification, and characterization of novel human  
polynucleotides encoding proteins that share sequence similarity  
with mammalian SEL-1 proteins. The invention encompasses the  
described polynucleotides, host cell expression systems, the  
encoded proteins, fusion proteins, polypeptides and peptides,  
15 antibodies to the encoded proteins and peptides, and genetically  
engineered animals that either lack or over express the disclosed  
genes, antagonists and agonists of the proteins, and other  
compounds that modulate the expression or activity of the proteins  
encoded by the disclosed genes that can be used for diagnosis,  
20 drug screening, clinical trial monitoring and the treatment of  
physiological disorders.

2. BACKGROUND OF THE INVENTION

SEL-1 proteins are negative regulators of *Notch* family  
receptors. *Notch* receptors and their associated signaling  
25 pathways have been associated with development, apoptosis, neuron  
growth and maintenance. Genetic alterations in *Notch* receptors  
and their ligands have been associated with multiple human  
processes and disorders such as diabetes, cancer (*inter alia*  
pancreatic cancer and insulinomas), stroke, Alzheimer's and other  
30 neurodegenerative diseases, cholesterol and fat metabolism (HMG  
CoA reductase degradation), blood pressure abnormalities, Coronary

artery disease and immunity (Donoviel and Bernstein, WO 99/27088, incorporated by reference in its entirety).

### 3. SUMMARY OF THE INVENTION

5       The present invention relates to the discovery, identification, and characterization of nucleotides that encode novel human proteins, and the corresponding amino acid sequences of these proteins. The novel human proteins (NHPs) described for the first time herein share structural similarity with animal  
10   *Notch* ligands, and particularly SEL-1. As such, the novel *Notch* ligand proteins represent new members of the *Notch* ligand family, a family that has a range of homologues and orthologs that transcend phyla and species.

      The novel human nucleic acid sequences described herein,  
15   encode proteins/open reading frames (ORFs) of 689, 688, 590, 418, 499, 576, and 575 amino acids in length (see SEQ ID NOS: 2, 4, 6, 8, 10, 12, and 14 respectively).

      The invention also encompasses agonists and antagonists of the described NHPs, including small molecules, large molecules,  
20   mutant NHPs, or portions thereof that compete with native NHP, peptides, and antibodies, as well as nucleotide sequences that can be used to inhibit the expression of the described NHPs (e.g., antisense and ribozyme molecules, and gene or regulatory sequence replacement constructs) or to enhance the expression of the  
25   described NHP sequences (e.g., expression constructs that place the described sequence under the control of a strong promoter system), and transgenic animals that express a NHP transgene, or "knock-outs" (which can be conditional) that do not express a functional NHP.

30   Further, the present invention also relates to processes for identifying compounds that modulate, i.e., act as agonists or antagonists, of NHP expression and/or NHP activity that utilize purified preparations of the described NHPs and/or NHP product, or

cells expressing the same. Such compounds can be used as therapeutic agents for the treatment of any of a wide variety of symptoms associated with biological disorders, including, but not limited to, diabetes, heart disease and cancer.

5

#### 4. DESCRIPTION OF THE SEQUENCE LISTING AND FIGURES

The Sequence Listing provides the sequences of the NHP ORFs encoding the described NHP amino acid sequences.

#### 10 5. DETAILED DESCRIPTION OF THE INVENTION

The NHPs, described for the first time herein, are novel proteins that are expressed in, *inter alia*, human testis cells and gene trapped human cell lines. The present invention encompasses the nucleotides presented in the Sequence Listing, host cells  
15 expressing such nucleotides, the expression products of such nucleotides, and: (a) nucleotides that encode mammalian homologs of the described sequences, including the specifically described NHPs, and the NHP products; (b) nucleotides that encode one or more portions of the NHPs that correspond to functional domains,  
20 and the polypeptide products specified by such nucleotide sequences, including but not limited to the novel regions of any active domain(s); (c) isolated nucleotides that encode mutant versions, engineered or naturally occurring, of the described NHPs in which all or a part of at least one domain is deleted or  
25 altered, and the polypeptide products specified by such nucleotide sequences, including but not limited to soluble proteins and peptides in which all or a portion of the signal sequence is deleted; (d) nucleotides that encode chimeric fusion proteins containing all or a portion of a coding region of an NHP, or one  
30 of its domains (e.g., a receptor or ligand binding domain, accessory protein/self-association domain, etc.) fused to another peptide or polypeptide; or (e) therapeutic or diagnostic derivatives of the described polynucleotides such as

oligonucleotides, antisense polynucleotides, ribozymes, dsRNA, or gene therapy constructs comprising a sequence first disclosed in the Sequence Listing. As discussed above, the present invention includes: (a) the human DNA sequences presented in the Sequence

5 Listing (and vectors comprising the same) and additionally contemplates any nucleotide sequence encoding a contiguous NHP open reading frame (ORF) that hybridizes to a complement of a DNA sequence presented in the Sequence Listing under highly stringent conditions, e.g., hybridization to filter-bound DNA in 0.5 M  
10  $\text{NaHPO}_4$ , 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel F.M. et al., eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3) and encodes a functionally equivalent gene  
15 product. Additionally contemplated are any nucleotide sequences that hybridize to the complement of the DNA sequence that encode and express an amino acid sequence presented in the Sequence Listing under moderately stringent conditions, e.g., washing in 0.2xSSC/0.1% SDS at 42°C (Ausubel et al., 1989, *supra*), yet still  
20 encode a functionally equivalent NHP product. Functional equivalents of a NHP include naturally occurring NHPs present in other species and mutant NHPs whether naturally occurring or engineered (by site directed mutagenesis, gene shuffling, directed evolution as described in, for example, U.S. Patent No.  
25 5,837,458). The invention also includes degenerate nucleic acid variants of the disclosed NHP polynucleotide sequences.

Additionally contemplated are polynucleotides encoding NHP ORFs, or their functional equivalents, encoded by polynucleotide sequences that are about 99, 95, 90, or about 85 percent similar  
30 or identical to corresponding regions of the nucleotide sequences of the Sequence Listing (as measured by BLAST sequence comparison analysis using, for example, the GCG sequence analysis package using standard default settings).

The invention also includes nucleic acid molecules, preferably DNA molecules, that hybridize to, and are therefore the complements of, the described NHP nucleotide sequences. Such hybridization conditions may be highly stringent or less highly  
5 stringent, as described above. In instances where the nucleic acid molecules are deoxyoligonucleotides ("DNA oligos"), such molecules are generally about 16 to about 100 bases long, or about 20 to about 80, or about 34 to about 45 bases long, or any variation or combination of sizes represented therein that  
10 incorporate a contiguous region of sequence first disclosed in the Sequence Listing. Such oligonucleotides can be used in conjunction with the polymerase chain reaction (PCR) to screen libraries, isolate clones, and prepare cloning and sequencing templates, etc.

15 Alternatively, such NHP oligonucleotides can be used as hybridization probes for screening libraries, and assessing gene expression patterns (particularly using a micro array or high-throughput "chip" format). Additionally, a series of the described NHP oligonucleotide sequences, or the complements  
20 thereof, can be used to represent all or a portion of the described NHP sequences. The oligonucleotides, typically between about 16 to about 40 (or any whole number within the stated range) nucleotides in length may partially overlap each other and/or the NHP sequence may be represented using oligonucleotides that do not  
25 overlap. Accordingly, the described NHP polynucleotide sequences shall typically comprise at least about two or three distinct oligonucleotide sequences of at least about 18, and preferably about 25, nucleotides in length that are each first disclosed in the described Sequence Listing. Such oligonucleotide sequences  
30 may begin at any nucleotide present within a sequence in the Sequence Listing and proceed in either a sense (5'-to-3') orientation vis-a-vis the described sequence or in an antisense orientation.

For oligonucleotide probes, highly stringent conditions may refer, e.g., to washing in 6xSSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligos), 48°C (for 17-base oligos), 55°C (for 20-base oligos), and 60°C (for 23-base oligos). These nucleic acid molecules may encode or act as NHP gene antisense molecules, useful, for example, in NHP gene regulation (for and/or as antisense primers in amplification reactions of NHP nucleic acid sequences). With respect to NHP gene regulation, such techniques can be used to regulate biological functions. Further, such sequences may be used as part of ribozyme and/or triple helix sequences that are also useful for NHP gene regulation.

Inhibitory antisense or double stranded oligonucleotides can additionally comprise at least one modified base moiety which is selected from the group including but not limited to

5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl)uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide can also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide will comprise at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or any combination or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an  $\alpha$ -anomeric oligonucleotide. An  $\alpha$ -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Alternatively, double stranded RNA can be used to disrupt the expression and function of a targeted NHP.

Oligonucleotides of the invention can be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides can be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), and methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

Low stringency conditions are well known to those of skill in the art, and will vary predictably depending on the specific organisms from which the library and the labeled sequences are derived. For guidance regarding such conditions see, for example, Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual (and periodic updates thereof), Cold Springs Harbor Press, N.Y.; and Ausubel et al., 1989, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N.Y.



Alternatively, suitably labeled NHP nucleotide probes can be used to screen a human genomic library using appropriately stringent conditions or by PCR. The identification and characterization of human genomic clones is helpful for identifying polymorphisms (including, but not limited to, nucleotide repeats, microsatellite alleles, single nucleotide polymorphisms, or coding single nucleotide polymorphisms), determining the genomic structure of a given locus/allele, and designing diagnostic tests. For example, sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (e.g., splice acceptor and/or donor sites), etc., that can be used in diagnostics and pharmacogenomics.

Further, a NHP sequence homolog can be isolated from nucleic acid from an organism of interest by performing PCR using two degenerate or "wobble" oligonucleotide primer pools designed on the basis of amino acid sequences within the NHP products disclosed herein. The template for the reaction may be total RNA, mRNA, and/or cDNA obtained by reverse transcription of mRNA prepared from human or non-human cell lines or tissue known or suspected to express an allele of a NHP gene.

The PCR product can be subcloned and sequenced to ensure that the amplified sequences represent the sequence of the desired NHP. The PCR fragment can then be used to isolate a full length cDNA clone by a variety of methods. For example, the amplified fragment can be labeled and used to screen a cDNA library, such as a bacteriophage cDNA library. Alternatively, the labeled fragment can be used to isolate genomic clones via the screening of a genomic library.

PCR technology can also be used to isolate full length cDNA sequences. For example, RNA can be isolated, following standard procedures, from an appropriate cellular or tissue source (i.e.,

one known, or suspected, to express a NHP sequence, such as, for example, testis or pancreatic tissue). A reverse transcription (RT) reaction can be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis. The resulting RNA/DNA hybrid may then be "tailed" using a standard terminal transferase reaction, the hybrid may be digested with RNase H, and second strand synthesis may then be primed with a complementary primer. Thus, cDNA sequences upstream of the amplified fragment can be isolated. For a review of cloning strategies that can be used, see e.g., Sambrook et al., 1989, *supra*.

A cDNA encoding a mutant NHP sequence can be isolated, for example, by using PCR. In this case, the first cDNA strand may be synthesized by hybridizing an oligo-dT oligonucleotide to mRNA isolated from tissue known or suspected to be expressed in an individual putatively carrying a mutant NHP allele, and by extending the new strand with reverse transcriptase. The second strand of the cDNA is then synthesized using an oligonucleotide that hybridizes specifically to the 5' end of the normal gene. Using these two primers, the product is then amplified via PCR, optionally cloned into a suitable vector, and subjected to DNA sequence analysis through methods well known to those of skill in the art. By comparing the DNA sequence of the mutant NHP allele to that of a corresponding normal NHP allele, the mutation(s) responsible for the loss or alteration of function of the mutant NHP gene product can be ascertained.

Alternatively, a genomic library can be constructed using DNA obtained from an individual suspected of or known to carry a mutant NHP allele (e.g., a person manifesting a NHP-associated phenotype such as, for example, obesity, high blood pressure, an inflammatory disorder, etc.), or a cDNA library can be constructed using RNA from a tissue known, or suspected, to express a mutant NHP allele. A normal NHP gene, or any suitable fragment thereof,

can then be labeled and used as a probe to identify the corresponding mutant NHP allele in such libraries. Clones containing mutant NHP gene sequences can then be purified and subjected to sequence analysis according to methods well known to those skilled in the art.

Additionally, an expression library can be constructed utilizing cDNA synthesized from, for example, RNA isolated from a tissue known, or suspected, to express a mutant NHP allele in an individual suspected of or known to carry such a mutant allele.

In this manner, gene products made by the putatively mutant tissue can be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against a normal NHP product, as described below. (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Press, Cold Spring Harbor.)

Additionally, screening can be accomplished by screening with labeled NHP fusion proteins, such as, for example, alkaline phosphatase-NHP or NHP-alkaline phosphatase fusion proteins. In cases where a NHP mutation results in an expressed gene product with altered function (e.g., as a result of a missense or a frameshift mutation), polyclonal antibodies to a NHP are likely to cross-react with a corresponding mutant NHP gene product. Library clones detected via their reaction with such labeled antibodies can be purified and subjected to sequence analysis according to methods well known in the art.

The invention also encompasses (a) DNA vectors that contain any of the foregoing NHP coding sequences and/or their complements (i.e., antisense); (b) DNA expression vectors that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences (for example, baculo virus as described in U.S. Patent No. 5,869,336 herein incorporated by reference); (c) genetically engineered host cells that contain any of the foregoing NHP coding

sequences operatively associated with a regulatory element that directs the expression of the coding sequences in the host cell; and (d) genetically engineered host cells that express an endogenous NHP gene under the control of an exogenously introduced regulatory element (i.e., gene activation). As used herein, regulatory elements include, but are not limited to, inducible and non-inducible promoters, enhancers, operators and other elements known to those skilled in the art that drive and regulate expression. Such regulatory elements include but are not limited to the human cytomegalovirus (hCMV) immediate early gene, regulatable, viral elements (particularly retroviral LTR promoters), the early or late promoters of SV40 adenovirus, the lac system, the trp system, the TAC system, the TRC system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, the promoter for 3-phosphoglycerate kinase (PGK), the promoters of acid phosphatase, and the promoters of the yeast  $\alpha$ -mating factors.

Also encompassed by the present invention are novel protein constructs engineered in such a way that they facilitate transport of the NHP to the target site, to the desired organ, across the cell membrane and/or to the nucleus where the NHP can exert its function activity. This goal may be achieved by coupling of the NHP to a cytokine or other ligand that would direct the NHP to the target organ and facilitate receptor mediated transport across the membrane into the cytosol. Conjugation of NHPs to antibody molecules or their Fab fragments could be used to target cells bearing a particular epitope. Attaching the appropriate signal sequence to the NHP would also transport the NHP to the desired location within the cell. Alternatively targeting of NHP or its nucleic acid sequence might be achieved using liposome or lipid complex based delivery systems. Such technologies are described in U.S. Patents Nos. 4,594,595, 5,459,127, 5,948,767 and 6,110,490

and their respective disclosures which are herein incorporated by reference in their entirety.

The present invention also encompasses antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists and agonists of the NHP, as well as compounds or nucleotide constructs that inhibit expression of a NHP gene (transcription factor inhibitors, antisense and ribozyme molecules, or gene or regulatory sequence replacement constructs), or promote the expression of a NHP (e.g., expression constructs in which NHP coding sequences are operatively associated with expression control elements such as promoters, promoter/enhancers, etc.).

The NHPs or NHP peptides, NHP fusion proteins, NHP nucleotide sequences, antibodies, antagonists and agonists can be useful for the detection of mutant NHPs or inappropriately expressed NHPs for the diagnosis of disease. The NHP proteins or peptides, NHP fusion proteins, NHP nucleotide sequences, host cell expression systems, antibodies, antagonists, agonists and genetically engineered cells and animals can be used for screening for drugs (or high throughput screening of combinatorial libraries) effective in the treatment of the symptomatic or phenotypic manifestations of perturbing the normal function of NHP in the body. The use of engineered host cells and/or animals may offer an advantage in that such systems allow not only for the identification of compounds that bind to the endogenous receptor for an NHP, but can also identify compounds that trigger NHP-mediated activities or pathways.

Finally, the NHP products can be used as therapeutics. For example, soluble derivatives such as NHP peptides/domains corresponding the NHPs, NHP fusion protein products (especially NHP-Ig fusion proteins, i.e., fusions of a NHP, or a domain of a NHP, to an IgFc), NHP antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists or agonists (including compounds that modulate or act on downstream targets in a NHP-

mediated pathway) can be used to directly treat diseases or disorders. For instance, the administration of an effective amount of soluble NHP, or a NHP-IgFc fusion protein or an anti-idiotypic antibody (or its Fab) that mimics the NHP could activate or effectively antagonize the endogenous NHP receptor. Soluble NHPs can also be modified by proteolytic cleavage to active peptide products (e.g., any novel peptide sequence initiating at any one of the amino acids presented in the Sequence Listing and ending at any downstream amino acid). Such products or peptides can be further subject to modification such as the construction of NHP fusion proteins and/or can be derivatized by being combined with pharmaceutically acceptable agents such as, but not limited to, polyethylene glycol (PEG).

Nucleotide constructs encoding such NHP products can be used to genetically engineer host cells to express such products *in vivo*; these genetically engineered cells function as "bioreactors" in the body delivering a continuous supply of a NHP, a NHP peptide, or a NHP fusion protein to the body. Nucleotide constructs encoding functional NHPs, mutant NHPs, as well as antisense and ribozyme molecules can also be used in "gene therapy" approaches for the modulation of NHP expression. Thus, the invention also encompasses pharmaceutical formulations and methods for treating or preventing biological disorders such as, but not limited to, Alzheimer's Disease, diabetes, cancer, neurodegenerative diseases such as Parkinson's disease, stroke, vascular dementia, and conditions requiring modulation of fat and cholesterol metabolism such as coronary artery disease.

Various aspects of the invention are described in greater detail in the subsections below.

## 5.1 THE NHP SEQUENCES

The cDNA sequences and the corresponding deduced amino acid sequences of the described NHPs are presented in the Sequence Listing. The NHP nucleotides were obtained from human gene  
5 trapped sequence tags and cDNA clones from a human testis cDNA library. A coding region single nucleotide polymorphism was observed during the generation of the described NHPs which consists of an A-to-G (or vice-versa) transition at base number 1,177 of, for example, SEQ ID NO:1 which results the presence of  
10 an glu or a lys at corresponding amino acid position 393 of, for example, SEQ ID NO:2.

Because of the diverse activities that have been associated with *Notch* signaling pathways, *Notch* receptors, and their associated ligands and antagonists have been subject to intense  
15 scientific scrutiny. For examples of how the described NHPs, or related *Notch* receptors can be produced, antagonized, used, processed, applied, and delivered, see, for example, U.S. Patent Nos. 5,786,158 and 5,780,300, and 5,856,441 the disclosures of which are hereby incorporated by reference in their entirety.  
20 Given their structural relatedness to *Notch* ligands, the described NHPs are suitable for use and modification as contemplated for other *Notch* ligands and antagonists.

## 5.2 NHPS AND NHP POLYPEPTIDES

25 NHPs, polypeptides, peptide fragments, mutated, truncated, or deleted forms of the NHPs, and/or NHP fusion proteins can be prepared for a variety of uses. These uses include, but are not limited to, the generation of antibodies, as reagents in diagnostic assays, for the identification of other cellular gene  
30 products related to a NHP, as reagents in assays for screening for compounds that can be as pharmaceutical reagents useful in the therapeutic treatment of mental, biological, or medical disorders and disease.

The Sequence Listing discloses the amino acid sequences encoded by the described NHP encoding polynucleotides. The NHPs have initiator methionines in DNA sequence contexts consistent with a translation initiation site, and further incorporate a  
5 hydrophobic leader sequence characteristic of secreted or membrane associated proteins.

The NHP amino acid sequences of the invention include the amino acid sequence presented in the Sequence Listing as well as analogues and derivatives thereof. Further, corresponding NHP  
10 homologues from other species are encompassed by the invention. In fact, any NHP protein encoded by the NHP nucleotide sequences described above are within the scope of the invention, as are any novel polynucleotide sequences encoding all or any novel portion of an amino acid sequence presented in the Sequence Listing. The  
15 degenerate nature of the genetic code is well known, and, accordingly, each amino acid presented in the Sequence Listing, is generically representative of the well known nucleic acid "triplet" codon, or in many cases codons, that can encode the amino acid. As such, as contemplated herein, the amino acid  
20 sequences presented in the Sequence Listing, when taken together with the genetic code (see, for example, Table 4-1 at page 109 of "Molecular Cell Biology", 1986, J. Darnell et al. eds., Scientific American Books, New York, NY, herein incorporated by reference) are generically representative of all the various permutations and  
25 combinations of nucleic acid sequences that can encode such amino acid sequences.

The invention also encompasses proteins that are functionally equivalent to the NHPs encoded by the presently described nucleotide sequences as judged by any of a number of criteria,  
30 including, but not limited to, the ability to bind and cleave a substrate of a NHP, or the ability to effect an identical or complementary downstream pathway, or a change in cellular metabolism (e.g., proteolytic activity, ion flux, tyrosine



phosphorylation, etc.). Such functionally equivalent NHP proteins include, but are not limited to, additions or substitutions of amino acid residues within the amino acid sequence encoded by the NHP nucleotide sequences described above, but which result in a silent change, thus producing a functionally equivalent gene product. Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

A variety of host-expression vector systems can be used to express the NHP nucleotide sequences of the invention. Where, as in the present instance, the NHP peptide or polypeptide is thought to be a soluble or secreted molecule, the peptide or polypeptide can be recovered from the culture media. Alternatively, if the described NHP is membrane associated, as characteristic of some Notch ligands, a soluble derivative can be engineered by deleting a transmembrane domain. Such expression systems also encompass engineered host cells that express a NHP, or functional equivalent, *in situ*. Purification or enrichment of a NHP from such expression systems can be accomplished using appropriate detergents and lipid micelles and methods well known to those skilled in the art. However, such engineered host cells themselves may be used in situations where it is important not only to retain the structural and functional characteristics of the NHP, but to assess biological activity, e.g., in drug screening assays.

The expression systems that can be used for purposes of the invention include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing NHP nucleotide sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing NHP nucleotide sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing NHP sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing NHP nucleotide sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the NHP product being expressed. For example, when a large quantity of such a protein is to be produced for the generation of pharmaceutical compositions of or containing NHP, or for raising antibodies to a NHP, vectors that direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther *et al.*, 1983, EMBO J. 2:1791), in which a NHP coding sequence may be ligated individually into the vector in frame with the *lacZ* coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. 13:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. 264:5503-5509); and the like. pGEX

vectors (Pharmacia or American Type Culture Collection) can also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by  
5 adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. The PGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear  
10 polyhidrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. A NHP gene coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin  
15 promoter). Successful insertion of NHP gene coding sequence will result in inactivation of the polyhedrin gene and production of non-occluded recombinant virus (i.e., virus lacking the proteinaceous coat coded for by the polyhedrin gene). These recombinant viruses are then used to infect *Spodoptera frugiperda*  
20 cells in which the inserted gene is expressed (e.g., see Smith et al., 1983, J. Virol. 46: 584; Smith, U.S. Patent No. 4,215,051).

In mammalian host cells, a number of viral-based expression systems can be utilized. In cases where an adenovirus is used as an expression vector, the NHP nucleotide sequence of interest may  
25 be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will  
30 result in a recombinant virus that is viable and capable of expressing a NHP product in infected hosts (e.g., See Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA 81:3655-3659). Specific initiation signals may also be required for efficient translation

of inserted NHP nucleotide sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where an entire NHP gene or cDNA, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression  
5 vector, no additional translational control signals may be needed. However, in cases where only a portion of a NHP coding sequence is inserted, exogenous translational control signals, including, perhaps, the ATG initiation codon, must be provided. Furthermore, the initiation codon must be in phase with the reading frame of  
10 the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements,  
15 transcription terminators, etc. (See Bittner et al., 1987, Methods in Enzymol. 153:516-544).

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such  
20 modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell  
25 lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be  
30 used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, human cell lines.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the NHP sequences described above can be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the NHP product. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the NHP product.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler, et al., 1977, Cell 11:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1962, Proc. Natl. Acad. Sci. USA 48:2026), and adenine phosphoribosyltransferase (Lowy, et al., 1980, Cell 22:817) genes can be employed in tk<sup>-</sup>, hgp<sup>+</sup> or ap<sup>+</sup> cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler, et al., 1980, Natl. Acad. Sci. USA 77:3567; O'Hare, et al., 1981, Proc. Natl. Acad. Sci. USA 78:1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA 78:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin, et al.,

1981, J. Mol. Biol. 150:1); and hygro, which confers resistance to hygromycin (Santerre, et al., 1984, Gene 30:147).

Alternatively, any fusion protein can be readily purified by utilizing an antibody specific for the fusion protein being expressed. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht, et al., 1991, Proc. Natl. Acad. Sci. USA 88:8972-8976). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the gene's open reading frame is translationally fused to an amino-terminal tag consisting of six histidine residues. Extracts from cells infected with recombinant vaccinia virus are loaded onto Ni<sup>2+</sup>-nitriloacetic acid-agarose columns and histidine-tagged proteins are selectively eluted with imidazole-containing buffers.

### 5.3 ANTIBODIES TO NHP PRODUCTS

Antibodies that specifically recognize one or more epitopes of a NHP, or epitopes of conserved variants of a NHP, or peptide fragments of a NHP are also encompassed by the invention. Such antibodies include but are not limited to polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')<sub>2</sub> fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

The antibodies of the invention may be used, for example, in the detection of NHP in a biological sample and may, therefore, be utilized as part of a diagnostic or prognostic technique whereby patients may be tested for abnormal amounts of NHP. Such antibodies may also be utilized in conjunction with, for example, compound screening schemes for the evaluation of the effect of test compounds on expression and/or activity of a NHP gene product. Additionally, such antibodies can be used in conjunction

gene therapy to, for example, evaluate the normal and/or engineered NHP-expressing cells prior to their introduction into the patient. Such antibodies may additionally be used as a method for the inhibition of abnormal NHP activity. Thus, such  
5 antibodies may, therefore, be utilized as part of treatment methods.

For the production of antibodies, various host animals may be immunized by injection with the NHP, an NHP peptide (e.g., one corresponding to a functional domain of an NHP), truncated NHP  
10 polypeptides (NHP in which one or more domains have been deleted), functional equivalents of the NHP or mutated variant of the NHP. Such host animals may include but are not limited to pigs, rabbits, mice, goats, and rats, to name but a few. Various adjuvants may be used to increase the immunological  
15 response, depending on the host species, including but not limited to Freund's adjuvant (complete and incomplete), mineral salts such as aluminum hydroxide or aluminum phosphate, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, and  
20 potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. Alternatively, the immune response could be enhanced by combination and or coupling with molecules such as keyhole limpet hemocyanin, tetanus toxoid, diphtheria toxoid, ovalbumin, cholera toxin  
25 or fragments thereof. Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of the immunized animals.

Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, can be obtained by any  
30 technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, (1975, Nature 256:495-497; and U.S. Patent No. 4,376,110), the human B-

cell hybridoma technique (Kosbor et al., 1983, Immunology Today 4:72; Cole et al., 1983, Proc. Natl. Acad. Sci. USA 80:2026-2030), and the EBV-hybridoma technique (Cole et al., 1985, Monoclonal Antibodies And Cancer Therapy, Alan R. Liss, Inc., pp. 77-96).

5 Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated in vitro or in vivo. Production of high titers of mAbs in vivo makes this the presently preferred method of production.

10 In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., 1984, Proc. Natl. Acad. Sci., 81:6851-6855; Neuberger et al., 1984, Nature, 312:604-608; Takeda et al., 1985, Nature, 314:452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity  
15 together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region.  
20 Such technologies are described in U.S. Patents Nos. 6,075,181 and 5,877,397 and their respective disclosures which are herein incorporated by reference in their entirety.

Alternatively, techniques described for the production of  
25 single chain antibodies (U.S. Patent 4,946,778; Bird, 1988, Science 242:423-426; Huston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; and Ward et al., 1989, Nature 334:544-546) can be adapted to produce single chain antibodies against NHP gene products. Single chain antibodies are formed by linking the heavy  
30 and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, such fragments



include, but are not limited to: the F(ab')<sub>2</sub> fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the F(ab')<sub>2</sub> fragments. Alternatively, Fab expression  
5 libraries may be constructed (Huse et al., 1989, Science, 246:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Antibodies to a NHP can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" a given NHP, using  
10 techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, 1993, FASEB J 7(5):437-444; and Nissinoff, 1991, J. Immunol. 147(8):2429-2438). For example antibodies which bind to a NHP domain and competitively inhibit the binding of NHP to its cognate receptor can be used to generate anti-idiotypes that  
15 "mimic" the NHP and, therefore, bind and activate or neutralize a receptor. Such anti-idiotypic antibodies or Fab fragments of such anti-idiotypes can be used in therapeutic regimens involving a NHP-mediated pathway.

The present invention is not to be limited in scope by the  
20 specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will  
25 become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims. All cited publications, patents, and patent applications are herein incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in the NHP sequence described in SEQ ID NO:1.
2. An isolated nucleic acid molecule comprising a nucleotide sequence that:
  - (a) encodes the amino acid sequence shown in SEQ ID NO:2; and
  - (b) hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.
3. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:4.
4. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:6.
5. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:8.
6. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:10.

# **ABSTRACT**

Novel human polynucleotide and polypeptide sequences are disclosed that can be used in therapeutic, diagnostic, and pharmacogenomic applications.

# PATENT APPLICATION

## DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

ATTORNEY DOCKET NO. 1 EX-0091-USA

As a below named inventor, I hereby declare that:

My residence/post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Novel Human Notch Ligand Proteins and Polynucleotides Encoding the Same

the specification of which is attached hereto unless the following box is checked:

( ) was filed on \_\_\_\_\_ as US Application Serial No. or PCT International Application

Number \_\_\_\_\_ and was amended on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

### Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
			YES: _____ NO: _____
			YES: _____ NO: _____

### Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE
60/165,959	11/17/1999

### U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS(patented/pending/abandoned)

### POWER OF ATTORNEY:

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) listed below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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(281) 362-6554

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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# SEQUENCE LISTING

<110> Turner, C. Alexander Jr.  
Nehls, Michael C.  
Friedrich, Glenn  
Zambrowicz, Brian  
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<120> Novel Human Notch Ligand Proteins and Polynucleotides  
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 Asn Leu Ala Tyr Met Tyr Glu His Gly Leu Gly Ile Thr Lys Asp Ile  
 595 600 605  
 His Leu Ala Arg Arg Leu Tyr Asp Met Ala Ala Gln Thr Ser Pro Asp  
 610 615 620  
 Ala His Ile Pro Val Leu Phe Ala Val Met Lys Leu Glu Thr Thr His  
 625 630 635 640  
 Leu Leu Arg Asp Ile Leu Phe Phe Asn Gln Phe Thr Thr Arg Trp Asn  
 645 650 655  
 Trp Leu Lys Leu Asp Asn Thr Ile Gly Pro His Trp Asp Leu Phe Val  
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 <213> Homo sapiens

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Arg Asn Val Thr Thr Gln Val Ser Val Asn Glu Ile Lys Gln Tyr Leu  
35 40 45  
Ser His Ile Leu Glu Gln Arg Thr Ser Ser Asn Val Ile Asn Lys Arg  
50 55 60  
Glu Asn Leu Leu Glu Lys Lys Asn Gln Arg Lys Ile Arg Ile Lys  
65 70 75 80  
Gly Ile Gln Asn Lys Asp Ile Leu Lys Arg Asn Lys Asn His Leu Gln  
85 90 95  
Lys Gln Ala Glu Lys Asn Phe Thr Asp Glu Gly Asp Gln Leu Phe Lys  
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Ala	Met	Glu	Lys	Met	Ala	Asp	Ala	Leu	Leu	Phe	Gly	Asn	Phe	Gly	Val	
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Gln	Asn	Ile	Thr	Ala	Ala	Ile	Gln	Leu	Tyr	Glu	Ser	Leu	Ala	Lys	Glu	
			165						170					175		
Gly	Ser	Cys	Lys	Ala	Gln	Asn	Ala	Leu	Gly	Phe	Leu	Ser	Ser	Tyr	Gly	
		180						185					190			
Ile	Gly	Met	Glu	Tyr	Asp	Gln	Ala	Lys	Ala	Leu	Ile	Tyr	Tyr	Thr	Phe	
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Gly	Ser	Ala	Gly	Gly	Asn	Met	Met	Ser	Gln	Met	Ile	Leu	Gly	Tyr	Arg	
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Tyr	Leu	Ser	Gly	Ile	Asn	Val	Leu	Gln	Asn	Cys	Glu	Val	Ala	Leu	Ser	
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Tyr	Tyr	Lys	Lys	Val	Ala	Asp	Tyr	Ile	Ala	Asp	Thr	Phe	Glu	Lys	Ser	
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		260						265					270			
Leu	Ser	Ser	Asn	Ser	Glu	Ile	Leu	Asp	Trp	Asp	Ile	Tyr	Gln	Tyr	Tyr	
		275					280						285			
Lys	Phe	Leu	Ala	Glu	Arg	Gly	Asp	Val	Gln	Ile	Gln	Val	Ser	Leu	Gly	
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Gln	Leu	His	Leu	Ile	Gly	Arg	Lys	Gly	Leu	Asp	Gln	Asp	Tyr	Tyr	Lys	
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Ala	Leu	His	Tyr	Phe	Leu	Lys	Ala	Ala	Lys	Ala	Gly	Ser	Ala	Asn	Ala	
			325					330						335		
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Gln	Asn	Asn	Ala	Thr	Ala	Phe	Lys	Tyr	Phe	Ser	Met	Ala	Ala	Ser	Lys	
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Gly	Asn	Ala	Ile	Gly	Leu	His	Gly	Leu	Gly	Leu	Leu	Tyr	Phe	His	Gly	
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Lys	Gly	Val	Pro	Leu	Asn	Tyr	Ala	Glu	Ala	Leu	Lys	Tyr	Phe	Gln	Lys	
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Ala	Ala	Glu	Lys	Gly	Trp	Pro	Asp	Ala	Gln	Phe	Gln	Leu	Gly	Phe	Met	
			405						410					415		
Tyr	Tyr	Ser	Gly	Ser	Gly	Ile	Trp	Lys	Asp	Tyr	Lys	Leu	Ala	Phe	Lys	
		420						425					430			
Tyr	Phe	Tyr	Leu	Ala	Ser	Gln	Ser	Gly	Gln	Pro	Leu	Ala	Ile	Tyr	Tyr	
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Leu	Ala	Lys	Met	Tyr	Ala	Thr	Gly	Thr	Gly	Val	Val	Arg	Ser	Cys	Arg	
	450					455					460					
Thr	Ala	Val	Glu	Leu	Tyr	Lys	Gly	Val	Cys	Glu	Leu	Gly	His	Trp	Ala	
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Glu	Lys	Phe	Leu	Thr	Ala	Tyr	Phe	Ala	Tyr	Lys	Asp	Gly	Asp	Ile	Asp	
			485					490						495		
Ser	Ser	Leu	Val	Gln	Tyr	Ala	Leu	Leu	Ala	Glu	Met	Gly	Tyr	Glu	Val	
		500					505						510			
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	515					520						525				
Leu	Glu	Lys	Glu	Lys	Met	Tyr	Pro	Met	Ala	Leu	Leu	Leu	Trp	Asn	Arg	
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 <212> PRT  
 <213> Homo sapiens

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 Arg Asn Val Thr Thr Gln Val Ser Val Asn Glu Ile Lys Gln Tyr Leu  
 35 40 45  
 Ser His Ile Leu Glu Gln Arg Thr Ser Ser Asn Val Ile Asn Lys Arg  
 50 55 60  
 Glu Asn Leu Leu Glu Lys Lys Asn Gln Arg Lys Ile Arg Ile Lys  
 65 70 75 80  
 Gly Ile Gln Asn Lys Asp Ile Leu Lys Arg Asn Lys Asn His Leu Gln  
 85 90 95  
 Lys Gln Ala Glu Lys Asn Phe Thr Asp Glu Gly Asp Gln Leu Phe Lys  
 100 105 110  
 Met Gly Ile Lys Val Leu Gln Gln Ser Lys Ser Gln Lys Gln Lys Glu  
 115 120 125  
 Glu Ala Tyr Leu Leu Phe Ala Lys Ala Ala Asp Met Gly Asn Leu Lys  
 130 135 140  
 Ala Met Glu Lys Met Ala Asp Ala Leu Leu Phe Gly Asn Phe Gly Val  
 145 150 155 160  
 Gln Asn Ile Thr Ala Ala Ile Gln Leu Tyr Glu Ser Leu Ala Lys Glu  
 165 170 175  
 Gly Ser Cys Lys Ala Gln Asn Ala Leu Gly Phe Leu Ser Ser Tyr Gly  
 180 185 190  
 Ile Gly Met Glu Tyr Asp Gln Ala Lys Ala Leu Ile Tyr Tyr Thr Phe  
 195 200 205  
 Gly Ser Ala Gly Gly Asn Met Met Ser Gln Met Ile Leu Gly Tyr Arg  
 210 215 220  
 Tyr Leu Ser Gly Ile Asn Val Leu Gln Asn Cys Glu Val Ala Leu Ser  
 225 230 235 240  
 Tyr Tyr Lys Lys Val Ala Asp Tyr Ile Ala Asp Thr Phe Glu Lys Ser  
 245 250 255  
 Glu Gly Val Pro Val Glu Lys Val Arg Leu Thr Glu Arg Pro Glu Asn  
 260 265 270  
 Leu Ser Ser Asn Ser Glu Ile Leu Asp Trp Asp Ile Tyr Gln Tyr Tyr  
 275 280 285  
 Lys Phe Leu Ala Glu Arg Gly Asp Val Gln Ile Gln Val Ser Leu Gly  
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 Gln Leu His Leu Ile Gly Arg Lys Gly Leu Asp Gln Asp Tyr Tyr Lys  
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 325 330 335  
 Met Ala Phe Ile Gly Lys Met Tyr Leu Glu Gly Asn Ala Ala Val Pro  
 340 345 350  
 Gln Asn Asn Ala Thr Ala Phe Lys Tyr Phe Ser Met Ala Ala Ser Lys  
 355 360 365  
 Gly Asn Ala Ile Gly Leu His Gly Leu Gly Leu Leu Tyr Phe His Gly  
 370 375 380  
 Lys Gly Val Pro Leu Asn Tyr Ala Glu Ala Leu Lys Tyr Phe Gln Lys

385 390 395 400  
 Ala Ala Glu Lys Gly Trp Pro Asp Ala Gln Phe Gln Leu Gly Phe Met  
 405 410 415  
 Tyr Tyr Ser Gly Ser Gly Ile Trp Lys Asp Tyr Lys Leu Ala Phe Lys  
 420 425 430  
 Tyr Phe Tyr Leu Ala Ser Gln Ser Gly Gln Pro Leu Ala Ile Tyr Tyr  
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 Leu Ala Lys Met Tyr Ala Thr Gly Thr Gly Val Val Arg Ser Cys Arg  
 450 455 460  
 Thr Ala Val Glu Leu Tyr Lys Gly Val Cys Glu Leu Gly His Trp Ala  
 465 470 475 480  
 Glu Lys Phe Leu Thr Ala Tyr Phe Ala Tyr Lys Asp Gly Asp Ile Asp  
 485 490 495  
 Ser Ser Leu Val Gln Tyr Ala Leu Leu Ala Glu Met Gly Tyr Glu Val  
 500 505 510  
 Ala Gln Ser Asn Ser Ala Phe Ile Leu Glu Ser Lys Lys Ala Asn Ile  
 515 520 525  
 Leu Glu Lys Glu Lys Met Tyr Pro Met Ala Leu Leu Leu Trp Asn Arg  
 530 535 540  
 Ala Ala Ile Gln Gly His Ser Leu Gly Gln Lys Ile Val Arg His Gly  
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 Cys Ser Asn Glu Ser Arg Cys Pro His Thr Cys Ala Leu Cys Arg His  
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 Glu Thr Gly Asn Tyr Ala Phe Ala Pro Gly Tyr Pro Val Phe  
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<211> 1257

<212> DNA

<213> Homo sapiens

<400> 7

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atcaataaaa	gagaaaatct	cctggagaaa	aagaagaatc	aacgtaaaaa	aagaataaaa	240
ggaattcaaa	ataaagatat	cttgaagaga	aataagaatc	atttacaana	gcaagcagag	300
aaaaatttta	cagatgaagg	agaccagcta	tttaagatgg	gcatacaagg	tctccagcag	360
cttaaaagcc	aaaaacaaaa	agaagaagcc	tacctacttt	ttgccaaagc	agctgacatg	420
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tactttttca	tggcagccag	taagggcaat	gcaatcgccc	ttcatgggct	tggtttctct	1140
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 <212> PRT  
 <213> Homo sapiens

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 Arg Asn Val Thr Thr Gln Val Ser Val Asn Glu Ile Lys Gln Tyr Leu  
 35 40 45  
 Ser His Ile Leu Glu Gln Arg Thr Ser Ser Asn Val Ile Asn Lys Arg  
 50 55 60  
 Glu Asn Leu Leu Glu Lys Lys Asn Gln Arg Lys Ile Arg Ile Lys  
 65 70 75 80  
 Gly Ile Gln Asn Lys Asp Ile Leu Lys Arg Asn Lys Asn His Leu Gln  
 85 90 95  
 Lys Gln Ala Glu Lys Asn Phe Thr Asp Glu Gly Asp Gln Leu Phe Lys  
 100 105 110  
 Met Gly Ile Lys Val Leu Gln Gln Ser Lys Ser Gln Lys Gln Lys Glu  
 115 120 125  
 Glu Ala Tyr Leu Leu Phe Ala Lys Ala Ala Asp Met Gly Asn Leu Lys  
 130 135 140  
 Ala Met Glu Lys Met Ala Asp Ala Leu Leu Phe Gly Asn Phe Gly Val  
 145 150 155 160  
 Gln Asn Ile Thr Ala Ala Ile Gln Leu Tyr Glu Ser Leu Ala Lys Glu  
 165 170 175  
 Gly Ser Cys Lys Ala Gln Asn Ala Leu Gly Phe Leu Ser Ser Tyr Gly  
 180 185 190  
 Ile Gly Met Glu Tyr Asp Gln Ala Lys Ala Leu Ile Tyr Tyr Thr Phe  
 195 200 205  
 Gly Ser Ala Gly Gly Asn Met Met Ser Gln Met Ile Leu Gly Tyr Arg  
 210 215 220  
 Tyr Leu Ser Gly Ile Asn Val Leu Gln Asn Cys Glu Val Ala Leu Ser  
 225 230 235 240  
 Tyr Tyr Lys Lys Val Ala Asp Tyr Ile Ala Asp Thr Phe Glu Lys Ser  
 245 250 255  
 Glu Gly Val Pro Val Glu Lys Val Arg Leu Thr Glu Arg Pro Glu Asn  
 260 265 270  
 Leu Ser Ser Asn Ser Glu Ile Leu Asp Trp Asp Ile Tyr Gln Tyr Tyr  
 275 280 285  
 Lys Phe Leu Ala Glu Arg Gly Asp Val Gln Ile Gln Val Ser Leu Gly  
 290 295 300  
 Gln Leu His Leu Ile Gly Arg Lys Gly Leu Asp Gln Asp Tyr Tyr Lys  
 305 310 315 320  
 Ala Leu His Tyr Phe Leu Lys Ala Ala Lys Ala Gly Ser Ala Asn Ala  
 325 330 335  
 Met Ala Phe Ile Gly Lys Met Tyr Leu Glu Gly Asn Ala Ala Val Pro  
 340 345 350  
 Gln Asn Asn Ala Thr Ala Phe Lys Tyr Phe Ser Met Ala Ala Ser Lys  
 355 360 365  
 Gly Asn Ala Ile Gly Leu His Gly Leu Gly Leu Leu Tyr Phe His Gly  
 370 375 380  
 Lys Gly Val Pro Leu Asn Tyr Ala Glu Ala Leu Lys Tyr Phe Gln Lys  
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Ala Ala Glu Lys Gly Trp Pro Asp Ala Gln Phe Gln Leu Gly Phe Met  
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 <211> 1500  
 <212> DNA  
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 atcaataaaa gagaaaatct cctggagaaa aagaagaatc aacgtaaaat aagaataaaa 240  
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 aaaaatttta cagatgaagg agaccagcta ttaagatgg gcatacaagg tctccagcag 360  
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 gcccaaaacg cattaggatt tttgtcttct tatggaatag gaatggaata tgatcaagct 600  
 aaggcactga tatattacac ctttgggaagt gctggaggaa acatgatgtc ccagatgatt 660  
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 <211> 499  
 <212> PRT  
 <213> Homo sapiens

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 Arg Asn Val Thr Thr Gln Val Ser Val Asn Glu Ile Lys Gln Tyr Leu  
 35 40 45  
 Ser His Ile Leu Glu Gln Arg Thr Ser Ser Asn Val Ile Asn Lys Arg  
 50 55 60  
 Glu Asn Leu Leu Glu Lys Lys Lys Asn Gln Arg Lys Ile Arg Ile Lys  
 65 70 75 80  
 Gly Ile Gln Asn Lys Asp Ile Leu Lys Arg Asn Lys Asn His Leu Gln  
 85 90 95

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Lys Gln Ala Glu Lys Asn Phe Thr Asp Glu Gly Asp Gln Leu Phe Lys  
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 Met Gly Ile Lys Val Leu Gln Gln Ser Lys Ser Gln Lys Gln Lys Glu  
 115 120 125  
 Glu Ala Tyr Leu Leu Phe Ala Lys Ala Ala Asp Met Gly Asn Leu Lys  
 130 135 140  
 Ala Met Glu Lys Met Ala Asp Ala Leu Leu Phe Gly Asn Phe Gly Val  
 145 150 155 160  
 Gln Asn Ile Thr Ala Ala Ile Gln Leu Tyr Glu Ser Leu Ala Lys Glu  
 165 170 175  
 Gly Ser Cys Lys Ala Gln Asn Ala Leu Gly Phe Leu Ser Ser Tyr Gly  
 180 185 190  
 Ile Gly Met Glu Tyr Asp Gln Ala Lys Ala Leu Ile Tyr Tyr Thr Phe  
 195 200 205  
 Gly Ser Ala Gly Gly Asn Met Met Ser Gln Met Ile Leu Gly Tyr Arg  
 210 215 220  
 Tyr Leu Ser Gly Ile Asn Val Leu Gln Asn Cys Glu Val Ala Leu Ser  
 225 230 235 240  
 Tyr Tyr Lys Lys Val Ala Asp Tyr Ile Ala Asp Thr Phe Glu Lys Ser  
 245 250 255  
 Glu Gly Val Pro Val Glu Lys Val Arg Leu Thr Glu Arg Pro Glu Asn  
 260 265 270  
 Leu Ser Ser Asn Ser Glu Ile Leu Asp Trp Asp Ile Tyr Gln Tyr Tyr  
 275 280 285  
 Lys Phe Leu Ala Glu Arg Gly Asp Val Gln Ile Gln Val Ser Leu Gly  
 290 295 300  
 Gln Leu His Leu Ile Gly Arg Lys Gly Leu Asp Gln Asp Tyr Tyr Lys  
 305 310 315 320  
 Ala Leu His Tyr Phe Leu Lys Ala Ala Lys Ala Gly Ser Ala Asn Ala  
 325 330 335  
 Met Ala Phe Ile Gly Lys Met Tyr Leu Glu Gly Asn Ala Ala Val Pro  
 340 345 350  
 Gln Asn Asn Ala Thr Ala Phe Lys Tyr Phe Ser Met Ala Ala Ser Lys  
 355 360 365  
 Gly Asn Ala Ile Gly Leu His Gly Leu Gly Leu Leu Tyr Phe His Gly  
 370 375 380  
 Lys Gly Val Pro Leu Asn Tyr Ala Glu Ala Leu Lys Tyr Phe Gln Lys  
 385 390 395 400  
 Ala Ala Glu Lys Gly Trp Pro Asp Ala Gln Phe Gln Leu Gly Phe Met  
 405 410 415  
 Tyr Tyr Ser Gly Ser Gly Ile Trp Lys Asp Tyr Lys Leu Ala Phe Lys  
 420 425 430  
 Tyr Phe Tyr Leu Ala Ser Gln Ser Gly Gln Pro Leu Ala Ile Tyr Tyr  
 435 440 445  
 Leu Ala Lys Met Tyr Ala Thr Gly Thr Gly Val Val Arg Ser Cys Arg  
 450 455 460  
 Thr Ala Val Glu Lys Arg Leu Thr Phe Leu Lys Lys Arg Arg Cys Ile  
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 Gln Trp Arg Phe Ser Tyr Gly Ile Glu Leu Pro Phe Lys Ala Met His  
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<210> 11

<211> 1731



<212> DNA  
<213> Homo sapiens

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